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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/341,829	Lethe et al
Examiner	**Art Unit**
Minh-Tam Davis	1642

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Jan 22, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 16-22, 24, 26, 29, 33-38, 43, 45, 47, 49, and 53-56* is/are pending in the application.

4a) Of the above, claim(s) *4, 5, 20-22, 24, 26, 29, 33-37, 43, 45, 47, 49, and* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 6, 7, 16-19, 38, and 53* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) X Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-3, 6-7, 17-19, 38, 53, SEQ ID NO:4 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the Examiner has not followed the International Searching Authority, and International Preliminary Examining Authority regarding unity of the invention, as evidenced by the absence of invitations to pay additional fees. Further, MPEP 1850 states that up to 10 nucleotide sequences could be examined in a single application without restriction. In addition, it would not be a burden for the Examiner to search alL the sequences because the nucleotide and amino acid sequences whicH form the basis of the claimed invention are so highly related.

This is not found persuasive because the claimed nucleic acid molecule, i.e. a nucleic acid molecule which hybridizes under stringent conditions to SEQ ID NO:4, wherein said nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8, is known in the art (see 102 rejection), and thus would not form a special technical feature linking the claims of groups II-XXXXX. Further, due to the complex nature of the claimed material, it is proper to restrict the invention to one sequence. See MPEP 803.04. Moreover, since MPEP 1850 only states that "up" to 10 independent and distinct sequences will be examined in a single application without restriction, the exact number of sequences to be examined is not required.

After review and reconsideration, however, groups III-V, drawn to nucleic acid encoding various fragments of SEQ ID NO:5 recited in claim 24, is rejoined, as species, with group I.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-3, 6-7, 17-19, 38, and 53, SEQ ID NO: 4 are examined in the instant application. It is noted that claim 38 is examined only to the extent of a method for diagnosing a disorder using an agent that selectively binds the isolated nucleic acid molecule of claim 1, and not a method for diagnosing a disorder using an agent that selectively binds an expression product of the nucleic acid molecule of claim 1.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is indefinite for the use of the language "characterized". It is not clear what "characterized" means.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

1. Claims 1, 7, 17-19, 38, 53 are rejected under 112, first paragraph.

Claims 1, 7, 17-19, 38, 53 are drawn to a) an isolated nucleic acid molecule that hybridizes under stringent conditions to SEQ ID NO:4, b) nucleic acid molecules that differ from the nucleic acid molecule of (a) in codon sequence due to the degeneracy of the genetic code, and c) complements of (a) and (b), or complements of unique fragments of SEQ ID NO:4. Said isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8. The claims are further drawn to vectors comprising the above sequences and host cells transfected with them.

The specification discloses an isolated cDNA sequence, SEQ ID NO: 4, which encodes a predictive polypeptide sequence, SEQ ID NO. 5.

It is noted that a sequence unrelated to SEQ ID NO:4 could hybridize under stringent conditions to SEQ ID NO:4 via only a few nucleotides. Further, a complement could be partial or complete complement, wherein the partial complement could be complementary to the claimed sequence via only a few complementary nucleotides. The claims, as written, thus, encompass polynucleotides which vary substantially in length and also in nucleotide composition. The broadly claimed genus additionally, encompasses SEQ ID NO:4, as well as genes incorporating only portions of the disclosed sequence.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the

genus or of a recitation of structural freatures common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural freatures that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Thus, only isolated DNA molecules consisting of SEQ ID NO: 4, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

2. Claim 6 is rejected under 112, first paragraph.

Claim 6 is drawn to an allelic variant of a LAGE-1 nucleic acid molecule.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself

is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for variants is provided in the specification on page 18. However, no disclosure, beyond the mere mention of allelic variants in claim 6 is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The instant specification fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and

there is no information regarding the relation of structure to function. Structural freatures that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:4 and equivalent degenerative codon sequences thereof, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

1. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 38 is drawn to a method for diagnosing a disorder using an agent that selectively binds a) a nucleic acid molecule which hybridizes under stringent conditions to SEQ ID NO:4, or b) nucleic acid molecules that differ from the above nucleic acid molecule of (a) in codon sequence due to the degeneracy of the genetic code, or c) complements of (a) or (b). Said nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

It is noted that an agent could be any compound, and that there are different degree of selectivity. Under low selectivity condition, any compound would bind to the claimed nucleic acid molecules. In addition, claim 38 reads on an agent that hybridizes to the claimed nucleic acid molecules, wherein hybridization conditions are not known. It is well known in the art that under low stringent hybridization conditions, any compound would bind to the claimed nucleic acid molecules. Given the broadest interpretation the claimed method would not detect any disease. Further, it is not clear whether there exists a probe specific for SEQ ID NO:4, because there is a very high homology between SEQ ID NO:4 and SEQ ID Nos: 6 and 8, and that among the probes that are specific for the LAGE-1 family, the probe BLE72 disclosed in the specification is not specific for SEQ ID NO:4, and would also detect SEQ ID NO:6 (see figure 1, and table II). The PCR probes BLE70 and BLE71 detect all three sequences of SEQ ID Nos: 4, 6 and 8.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

2. Claim 53 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 53 is drawn to a "vaccine" composition comprising a nucleic acid molecule encoding LAGE-1, which hybridizes under stringent conditions to SEQ ID NO:4, or b) nucleic acid molecules that differ from the above nucleic acid molecule of (a) in codon sequence due to the degeneracy of the genetic code, or c) complements of (a) or (b), or an immunogenic fragment thereof. Said isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

The specification contemplates the use of the claimed nucleic acid molecules for treating disorders characterized by expression of the claimed nucleic acid molecule, wherein said disorders could be cancer or melanoma in particular (p.28).

The specification provides no exemplification of or guidance on how to use the claimed vaccine formulation for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among

patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which woul allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

3. Claims 1, 38 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 38 are drawn to nucleic acid molecules that differ from an isolated nucleic acid molecule, that hybridizes under stringent conditions to SEQ ID NO:4, in codon sequence due to the degeneracy of the genetic code, and a method for detecting a disorder by detecting said nucleic acid molecule. Said isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8. Claim 53 is drawn to a vaccine composition comprising a nucleic acid molecule encoding LAGE-1, which hybridizes under stringent conditions to SEQ ID NO:4, or b) nucleic acid molecules that differ from the above nucleic acid molecule of (a) in codon sequence due to the degeneracy of the genetic code, or c) complements of (a) or (b), or an immunogenic fragment thereof. Said isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

The specification discloses isolation of a cDNA sequence of SEQ ID NO:4, and detection of mRNA in tumors. The specification however does not disclose detection of the claimed LAGE-1 polypeptide in tumors. One cannot extrapolate the teaching of the specification to the enablement of the claims because there is no teaching of whether any protein product is actually produced in tumors. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For

example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to predict if SEQ ID NO:4 would in fact be translated into a polypeptide expression product in tumors. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention.

Further, the language "nucleic acid molecules that differ from an isolated nucleic acid molecule, that hybridizes under stringent conditions to SEQ ID NO:4, in codon sequence due to the degeneracy of the genetic code" reads on nucleic acid molecules that are obtained from back translation of SEQ ID NO:5, which is encoded by SEQ ID NO:4. Since it is unpredictable that SEQ ID NO:5 exists in nature, it is unpredictable that the claimed nucleic acid molecules that differ from an isolated nucleic acid molecule, that hybridizes under stringent conditions to SEQ ID NO:4, in codon sequence due to the degeneracy of the genetic code, exist in nature.

In addition, a fragment could be as little as one amino acid. There is no teaching of the characteristics of the claimed "immunogenic fragment", which would distinguish the claimed "fragment" from any other fragments of other sequences known in the art. Further, there is insufficient guidance regarding the parameters and sequence of peptides which correlate with the ability to stimulate and generate CTLs. There is insufficient guidance regarding selection of peptides that meet the instant criteria of generating CTLs. Since detailed information regarding the structural, and functional requirements and properties of the claimed "immunogenic fragment" are lacking, it would be undue experimentation for one of ordinary skill in the art to make and use the invention.

Moreover, as written, claim 53 drawn to a nucleic acid encoding an immunogenic fragment of LAGE-1 encompasses claims to defining a nucleic acid molecule encoding epitopes of a polypeptide. However, there is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology,

Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by the claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column).

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the claimed method employing all of the immunogenic fragments. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the encompassed fragments. Therefore, undue experimentation would be required to enable the claims as written.

4. Claims 3, 17-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 3 is drawn to an isolated nucleic acid molecule comprising "the coding region" of the nucleotide sequence of SEQ ID NO:4. The language "coding region" encompasses a nucleic acid molecule that is expressed as protein in nature. Claims 17-19 are drawn to an "expression vector" containing an isolated nucleic acid molecule that hybridizes under stringent conditions to SEQ ID NO:4, wherein said isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8, and a host cell containing the vector.

The specification discloses isolation of a cDNA sequence of SEQ ID NO:4, and detection of mRNA in tumors. The specification however does not disclose detection of the claimed LAGE-1 polypeptide in tumors. One cannot extrapolate the teaching of the specification to the enablement of the claims because it is unpredictable that whether any LAGE-1 protein product is actually produced in tumors, *supra*. Further, although using an expression vector and a host cell, expression of a vector containing the claimed nucleic acid molecule could produce a protein, however, since it is questionable that said protein exists in tumors, one of skill in the art would not know how to use said protein.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the encompassed encoded or expression product. Therefore, undue experimentation would be required to enable the claims as written.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, firs paragraph rejections, claims 1, 7, 16-19, 38 and 53 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule consisting of SEQ ID NO:4, does not reasonably provide enablement for an isolated nucleic acid molecule that hybridizes under stringent conditions to SEQ ID NO:4, b) nucleic acid molecules that differ from the nucleic acid molecule of (a) in codon sequence due to the degeneracy of the genetic code, and c) complements of (a) and (b), or complements of unique fragments of SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 1, 7, 16-19, 38, 53 are drawn to a) an isolated nucleic acid molecule that hybridizes under stringent conditions to SEQ ID NO:4, b) nucleic acid molecules that differ from the nucleic acid molecule of (a) in codon sequence due to the degeneracy of the genetic code, and c) complements of (a) and (b), or complements of unique fragments of SEQ ID NO:4. Said isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

The claims encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to the polynucleotide of SEQ ID NO:4, that encodes LAGE-1. That is polynucleotides that hybridize to said polynucleotides under stringent conditions, or complements thereof. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a

variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with polynucleotides.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, firs paragraph rejections, claims 1, 6 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule consisting of SEQ ID NO:4, does not reasonably provide enablement for an allelic variant of a LAGE-1 nucleic acid molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1 and 6 are drawn to an allelic variant of a LAGE-1 nucleic acid molecule.

It is pointed out that the term "variant" encompasses a variety of definitions, i.e. deletions, truncations, substitutions, conjugation, etc.. Applicant has not enabled these types of modified DNAs in the specification.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming

growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

3. If Applicant could overcome the above 112, firs paragraph rejections, claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule consisting of SEQ ID NO:4, does not reasonably provide enablement for a unique fragment of SEQ ID NO:4 between 12 and 992 nucleotides in length. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 7 is drawn to a unique fragment of SEQ ID NO:4 between 12 and 992 nucleotides in length.

The specification discloses that unique fragments are fragments that do not hybridize to or are the same as those in SEQ ID NO:8 (p.13). From sequence comparison between SEQ ID Nos: 4 and 8, it seems that the largest fragment of SEQ ID NO:4, that is not found in SEQ ID NO:8, is of 247 nucleotides in length, from nucleotide 756 to 1002 (MPSRCH search report, us-09-341-829a-8.res. pages 2-3). Thus it is not possible to have a unique fragment of SEQ ID NO:4 between 12 and 992 nucleotides in length.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

4. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting cancer, does not reasonably provide enablement for a method for detecting a disorder characterized by expression of LAGE-1 nucleic acid molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 38 is drawn to a method for diagnosing a disorder using an agent that selectively binds a) a nucleic acid molecule which hybridizes under stringent conditions to SEQ ID NO:4, or b) nucleic acid molecules that differ from the above nucleic acid molecule of (a) in codon sequence due to the degeneracy of the genetic code, or c) complements of (a) or (b). Said nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

The specification defines disorder as any pathological condition where the claimed nucleic acid molecule is expressed. The specification discloses overexpression of SEQ ID NO:4 in various

cancers. However, no disclosure is found in the specification concerning overexpression of SEQ ID NO:4 in any disease other than cancer.

One cannot extrapolate the teaching in the specification to the claim. It is unpredictable that SEQ ID NO:4 would express in tissues having diseases other than in cancer, because the role of SEQ ID NO:4 in different diseases is not known, and because there is no correlation between expression of SEQ ID NO:4 and any diseases other than cancer.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang, H et al, Genbank Sequence Database (Accession L39790), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available on 28 August, 1995.

Claim 1 is drawn to an isolated nucleic acid molecule that hybridizes under stringent conditions to SEQ ID NO:4, wherein said isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

Claim 7 is drawn to to a unique fragment of SEQ ID NO:4 between 12 and 992 nucleotides in length, and a complement thereof.

The specification discloses that unique fragments of SEQ ID NO:4 are fragments that do not hybridize to or are not the same as those in SEQ ID NO:8 (p.13).

Zhang et al teach a nucleotide sequence which is 100% similar to nucleotides 1-14 of SEQ ID NO:4. From sequence comparison between SEQ ID Nos: 4 and 8, it seems that the nucleotides 1-14 of SEQ ID NO:4 is not found in SEQ ID NO:8 (MPSRCH search report, us-09-341-829a-8.res, pages 2-3).

Thus the sequence taught by Zhang et al is the same as the claimed nucleic acid molecule of claim 1, because the inherent complement of the sequence taught by Zhang et al would hybridize under stringent condition to SEQ ID NO:4, wherein the inherent complement of the sequence taught by Zhang et al would exclude nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

Further, the sequence taught by Zhang et al is the same as the claimed unique fragment, as defined by the specification. The inherent complement of the sequence taught by Zhang et al is the same as the claimed complement of the unique fragment of claim 7.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of thisplication or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

May 15, 2001

SUSAN UNGAR, PH.D
PRIMARY EXAMINER